

**The Squarate
Ester–1,3,5,7-Octatetraene–Polyquinane Cascade:
Reaction Efficiency Is Intimately Linked to the
Locus of Substitution within the Vinyl Anion**

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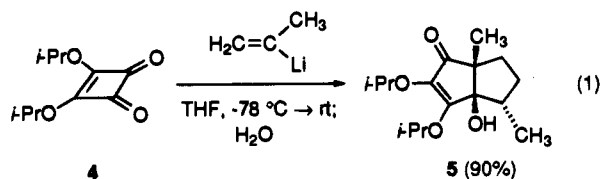
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The trans addition of two vinyl anions to a squarate ester is now recognized² to provide for ready conrotatory electrocyclicization with transient formation of a doubly-charged open-chain octatetraene exemplified by **1**. Subsequent orbital-symmetry-controlled 8π electrocyclization³ within **1** delivers dienolates such as **2**, which experience intramolecular aldolization to give **3** when protonated (Scheme 1). The lithium counterions may play an important role in directing the original nucleophilic attack from opposite π -faces and in facilitating both electrocyclic processes. In particular, the double lithium chelation shown for **1** may be especially critical in assuring the *s-cis* configuration required for ring closure.⁴ This remarkable sequence of operations is tolerant of two different anions and is capable of establishing many stereogenic centers from a triad of *achiral* reactants in a single laboratory operation. The very substantial increase in structural complexity, which results from the coupling of a stereoregulated bond cleavage to two subsequent, comparably restricted reconnection events, offers impressive synthetic potential.

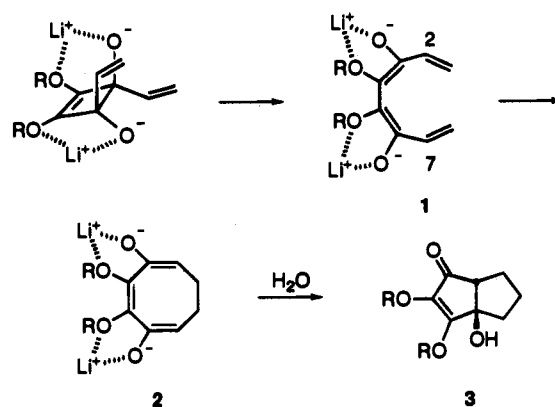
The classical stereochemical and kinetic studies of Huisgen³ and more recent theoretical investigations⁵ have demonstrated that the helical nature of 1,3,5,7-octatetraenes fosters conrotatory cyclization.⁶ Also, while a *trans* substituent at C-1 does not inhibit ring closure, a *cis* substituent at the same locale is rate retarding because steric crowding within the helix is somewhat exacerbated in the transition state. Although it is also recognized that 1,3,5-cyclooctatrienes are favored at equilibrium, this is the limit of our knowledge of these serviceable polyunsaturated intermediates.

The involvement of **1** in the title reaction was recognized to provide an opportunity to extend our appreciation of the reactivity of helical 1,3,5,7-octatetraenes. Herein we call attention to the strong interdependence of the efficiency of Scheme 1 and vinyl anion substitution. The use of >2 equiv of 2-propenyllithium places methyl groups at C-2 and C-7 in **1**. This is especially beneficial as reflected in the fact that the yield of **5** (90%) is twice that realized for **3** (R = *i*-Pr, 45%) under similar conditions (eq 1).

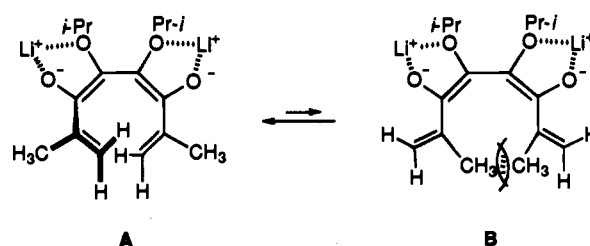


Comparable advantages surface when 1 equiv of a simple vinyl anion is added to **4** in advance of, or subsequent to, addition of cyclopentenyllithium (eqs 2–4). In the least

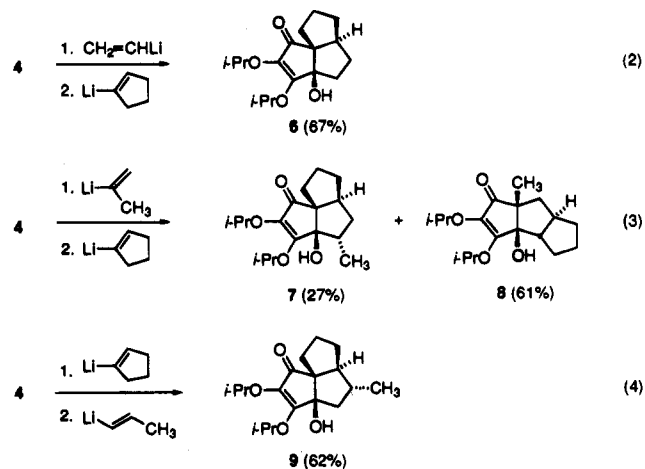
Scheme 1



Scheme 2



substituted example, the aldolization step is highly regioselective and **6** is produced uniquely (67%). The positioning of a methyl substituent at the nucleophilic carbon enhances the isolated yields significantly, although the final ring closure now occurs along dual paths to deliver both **7** (27%) and **8** (61%). Consideration of *trans*-propenyllithium (eq 4) made us aware that the cyclization of **1** can continue to operate *after this species is protonated*. Whereas workup immediately following quench-



ing gives **9** in a yield of 20%, storage of the aqueous THF solution overnight under an inert atmosphere prior to product isolation leads to a dramatic improvement in the amount of **9** obtained (62%). This finding is consistent with the notion that neutralized **1** achieves a reasonable level of enol character. Note

(1) National Needs Fellow, 1991–1994.
(2) Negri, J. T.; Morwick, T.; Doyon, J.; Wilson, P. D.; Hickey, E. R.; Paquette, L. A. *J. Am. Chem. Soc.* **1993**, *115*, 12189.
(3) (a) Huisgen, R.; Dahmen, A.; Huber, H. *J. Am. Chem. Soc.* **1967**, *89*, 7130. (b) Huisgen, R.; Dahmen, A.; Huber, H. *Tetrahedron Lett.* **1969**, 1461. (c) Dahmen, A.; Huisgen, R. *Tetrahedron Lett.* **1969**, 1465.
(4) Cyclobutenediones carrying one or two non-alkoxy substituents have been noted to respond less efficiently to this series of reactions.

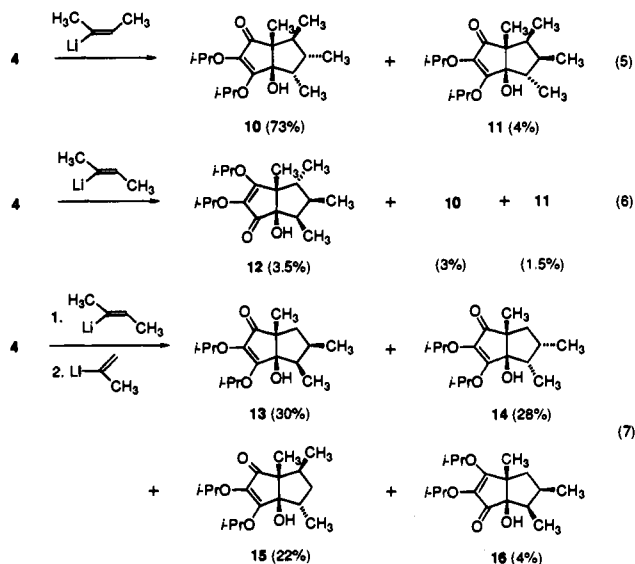
(5) Thomas, B. E., IV; Evanseck, J. D.; Houk, K. N. *J. Am. Chem. Soc.* **1993**, *115*, 4165. See also: Jiao, H.; Schleyer, P. v. R. *J. Chem. Soc., Perkin Trans. 2* **1994**, 407.

(6) See also: (a) Marvell, E. N.; Seubert, J.; Vogt, G.; Zimmer, G.; Moy, G.; Siegmann, J. R. *Tetrahedron* **1978**, *34*, 1323. (b) Nicolaou, K. C.; Petasis, N. A.; Zipkin, R. S.; Uenishi, J. *J. Am. Chem. Soc.* **1982**, *104*, 5555. (c) Nicolaou, K. C.; Zipkin, R. E.; Petasis, N. A. *J. Am. Chem. Soc.* **1982**, *104*, 5558. (d) Snider, B.; Harvey, T. C. *J. Org. Chem.* **1994**, *59*, 504.

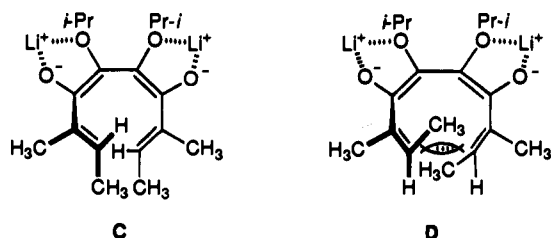
that the transannular aldol cyclization in eq 4 once again results from preferential attack on the less sterically congested carbonyl group.^{7,8}

As shown in Scheme 2, incorporation of a methyl group at C-2 and/or C-7 can be expected to favor the adoption of conformer **A** in order to avoid the nonbonded steric compression present in **B**. Stereoalignment of the terminal π bonds in the octatetraene intermediate is ideally served by the population of **A**.

To gain support for this mechanistic model, we have examined the consequences of adding >2 equivs of (*Z*)- and (*E*)-2-butenyllithium to **4** (eqs 5 and 6). In the first instance,



the requirements on the structure of the intermediate imposed by the *cis* disposition of the methyl groups point to the energetic feasibility of assuming torsional angles approximated by conformer **C**, with anticipated facilitation of closure to the cyclooctatriene. That a favorable state of affairs has indeed



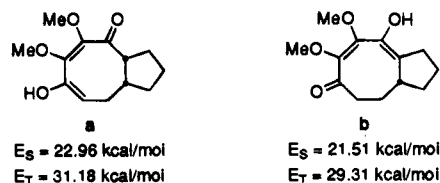
been realized is obvious from the 73% yield of **10** realized immediately after quenching. As before,² the small amount of **11** (4%) derives from *cis* addition. The efficiency of eq 5 is

not a function of the number of methyl substituents, as reflected by the realization of a maximum 8% combined yield of **10–12** (eq 6). The geometry of the *E* anion necessitates the evolution of **D**, whose all-*cis* conformation is quite sterically congested. Its attainability is therefore disadvantaged, and undesirable side reactions unrelated to 8π electrocyclicization become prevalent. As detailed in eq 7, a significant recouping of efficiency is possible if the second anion is 2-propenyl in nature and isolation is not performed until several hours after the introduction of saturated NH_4Cl solution with maintenance of an argon atmosphere. Diquinanes **13** (30%) and **14** (28%) are recognized to arise from a common monoprotanated intermediate which experiences transannular aldolization from two different π -faces. Product **15** (22%) derives from the second possible pre-aldol regioisomer, and **16** (4%) is the end result of 1,4-addition by the second vinyl anion.^{2,9}

In conclusion, the requirement that squarate esters pass through coiled 1,3,5,7-octatetraenes during conversion to polyquinanes provides an unrivaled opportunity for indirect evaluation of the reactivity of these intermediates. The present study establishes that dynamically equilibrating tetraene conformations are amenable to modulation by substitution. Further, insight is provided into the means for heightening population of the Möbius-like, all-*cis* arrangement uniquely conducive to conrotatory cyclization. Full appreciation of these factors is expected to lend itself nicely to the purposeful adoption of this "power reaction"¹⁰ in synthesis.¹¹

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(7) MM2 calculations dealing with the global minimum energy conformations of **a** and **b** indicate the latter to be *ca.* 1.9 kcal/mol more stable. The enolate anions corresponding to these structures are isoenergetic ($E_T = 44.5$ kcal/mol).



If the assumption is made that the rates of aldolization of **a** and **b** are roughly comparable and have no reversibility component, the observed aldol selectivity would be the result of a thermodynamic bias at the stage following neutralization.

(8) In the strictest sense, the degree of substitution present in **6–8** is inadequate to allow definition of the extent to which these products might be formed by tandem *cis*-addition/oxy-Cope rearrangement. We do recognize, however, that in the great majority of cases *trans* addition predominates for steric reasons (ref 2 and unpublished results).

(9) All new compounds reported herein have been fully characterized by IR, high-field ^1H and ^{13}C NMR, and high-resolution mass spectrometry and/or combustion analysis. The structural assignments to **5**, **8**, **9**, and **12** were secured by means of X-ray crystallography and to **7**, **10**, **11**, and **13–16** by 2-D NMR methods.

(10) Rawal, V. H.; Dufour, C. *J. Am. Chem. Soc.* **1994**, *116*, 2613.

(11) We thank the National Science Foundation for financial support, Professor Robin Rogers for the X-ray determinations, James Lanter for the MM2 calculations, Dr. Peter Wilson for first performing the experiment described in eq 2, and Dr. Conrad Kowalski (SmithKline Beecham Pharmaceuticals) for a gift of squaric acid.